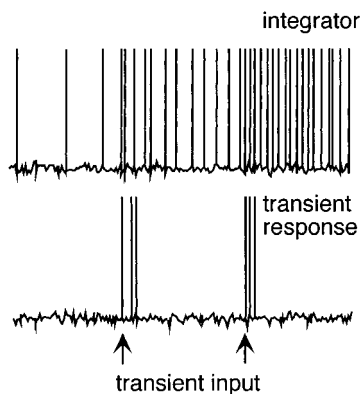


Integrating with Action Potentials

When we add a long list of numbers in our heads, we must keep track of the running total while performing the individual summations. Neural circuits integrating information must similarly retain a representation of what has been gathered up to a given point in time, so that this can be augmented by further information as it becomes available. Integration, the task of summing and accumulating a series of inputs, involves both computation (addition) and memory (retention of the sum). Models of neural circuits performing integration suggest that the memory part of the task is the more challenging to accomplish and difficult to understand.

There is considerable experimental evidence supporting the ability of neural circuits to act as integrators in tasks such as target selection (Schall and Thompson, 1999), sensory discrimination (Gold and Shadlen, 2000), and oculomotor control (Robinson, 1989). The oculomotor system is the subject of a theoretical study by Seung, Lee, Reis, and Tank appearing in this issue of *Neuron* (Seung et al., 2000). Neurons in the prepositus hypoglossi and medial vestibular nucleus of the mammalian oculomotor system, and in an analogous oculomotor circuit of the goldfish modeled by Seung et al., maintain, in their persistent activity, a memory trace of the horizontal position of the eyes. This information is obtained by integrating the transient outputs of burst neurons that signal changes in eye position. Brief pulses from the burst neurons shift the activity of the integrator neurons either upward or downward, and that activity is maintained between burst discharges as in the upper trace of the figure. Following a path set by earlier work (Robinson, 1989; Seung, 1996), Seung et al. show that integration can be achieved in a network of relatively realistic spiking model neurons.



Cartoon of the Activity of a Neuron in an Integrator Circuit

The arrows at the bottom represent transient input to a neural circuit. The two traces show different types of responses. The lower trace shows directly driven, transient responses similar to those of burst neurons in the oculomotor system. The upper trace shows a neuron that is part of a hypothetical integrator circuit. The firing rate is incremented by each transient input, and activity is sustained between the inputs at a level that reflects a running total of the input received. Other inputs, not shown here, can decrement the integrator.

The sustained activity seen in the oculomotor integrator, like that shown in the figure, provides a representation of the running integral of the burst neuron inputs. Similar types of sustained activity have been seen in a number of brain areas in monkeys doing tasks that require short-term memory of transient stimuli (Fuster, 1995). They have been interpreted in this context as a neural correlate of working memory (Goldman-Rakic, 1994; Fuster, 1995). Therefore, the question of what sustains this activity is important for understanding not only neural integrators, but potential mechanisms of short-term memory as well.

An idea going back to Hebb (1949) is that a persistent response to a transient input can be generated when feedback input from other neurons within an integrator or memory circuit substitutes for the transient external drive (Amit, 1989). For this mechanism to work, the recurrent connections within the circuit must provide each neuron with exactly what it needs to maintain an appropriate level of activity. This requirement is particularly stringent in an integrator circuit, as opposed to an associative memory network (Amit, 1989), because the integrator must be capable of sustaining activity at virtually any level to represent all values of the quantity being integrated. Not surprisingly, this requires some fine tuning. If neurons in the circuit receive slightly too much input from each other during the sustained period, network activity will rise, creating even more input. This can lead to uncontrolled growth of activity. If the recurrent excitation is too weak, the network will fail to sustain itself, and activity will decline to zero. The presence of inhibitory input shifts the point at which sustained firing occurs, but it does not alleviate the fine-tuning problem.

The goldfish oculomotor circuit being modeled by Seung et al. is not a perfect integrator, but it is remarkably good. The level of activity during sustained periods drifts with a time constant greater than 10 s. The time scale for the retention of activity in the absence of finely tuned recurrent excitation in the model of Seung et al. is roughly equal to the decay time of its excitatory synaptic conductances. This is set to 100 ms, similar to the decay time of NMDA conductances, which is obviously much shorter than the required 10 s. Increasing the decay time for self-sustained activity from 100 ms to greater than 10 s requires adjusting the network interactions to an accuracy better than 1%. Seung et al. achieved this fine tuning by performing a least-squares fit of the recurrent input generated by the circuit to the required input. Such a calculation is difficult in the type of spiking, conductance-based model they use. They therefore constructed an approximate description of their model in terms of firing rates and average synaptic inputs, and performed the matching calculation within the firing rate model. The firing rate model provides an accurate enough description of the spiking model that this procedure worked. This is a reassuring result for neural modelers who flip between spiking and firing rate descriptions of neural circuits in the belief that the two are in agreement. The final spiking model of the goldfish oculomotor integrator is sufficiently realistic to allow detailed comparison with experimental results. This should prove extremely valuable in the impressive ongoing combined theory and experimental investigation of this system

being conducted by Seung, Tank, and their collaborators.

Related results have been obtained in studies of sustained activity during working memory. While Seung et al. used a function matching approach, fine tuning in a spiking model of sustained activity has also been achieved by imposing a symmetry on the synaptic connections of a network (Compte et al., 2000). Symmetry, like function matching, assures that the network has the approximately continuous series of self-sustaining states needed to represent virtually any value of the quantity being integrated. Wang (1999) also noted the importance of using slow, NMDA-type synapses in these circuits to stabilize sustained activity.

The paper of Seung et al. shows that a spiking model integrator can work if: (1) excitatory synaptic conductances are slow, with dynamics resembling NMDA conductances, and (2) synaptic parameters are tuned to a sufficient degree of accuracy. Point 1 makes testable predictions. If excitatory transmission is glutamatergic, we would expect an abundance of NMDA-mediated synaptic transmission in integrator or persistent-memory circuits. Blocking this transmission should significantly degrade their function. Point 2 raises a number of interesting questions that will undoubtedly be addressed in future theoretical and experimental work. Do integrator circuits really have parameters tuned to a sufficient degree of accuracy? Do they make use of activity-dependent adjustment mechanisms that do the fine tuning automatically (Arnold and Robinson, 1992; Seung, 1996)? Or do integrators operate by a completely different principle, for example through intrinsic properties of the integrator neurons such as regenerative plateau potentials? The construction of reasonably realistic models that act as neural integrators does not answer these questions, but it is a significant advance nonetheless, because it tells us that they are the right questions to ask, and it provides a framework for proposing and interpreting future experiments. For example, the first two questions might be addressed by experiments that perturb synaptic strength and probe for resulting plasticity, while intracellular recordings could investigate the third.

Addressing the issue of stability of a neural integrator is important, even for researchers not interested in integrator circuits per se. Similar issues arise when we think of neural activity propagating from one region of the brain to another—for example, through the many visual areas in the mammalian brain. If the level of activity increased or decreased by even a modest percentage as visual responses propagated from one visual area to the next, the level of activity evoked in late-stage areas would be either pathologically high or nonexistent. The same unknown mechanisms that allow neural circuits to compute integrals may act on a larger scale to assure that an appropriate level of activity reaches all the relevant regions of the brain, a nontrivial but essential element of healthy brain function.

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